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EXAMINER	
MARVICH, MARIA	
ART UNIT	**PAPER NUMBER**
1636	9

DATE MAILED: 03/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/081,969	Applicant(s) CHENG ET AL.	
	Examiner Maria B Marvich, PhD	Art Unit 1636	

-- The MAILING DATE of this communication app ars on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-60 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) 1-3,5,6,8,9,11,14,16,17,38-43,45,48-51 and 58-59 is/are allowed.

6)☒ Claim(s) 4,7,10,12,13,15,18-37,44,46,47,52-57 and 60 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 22 February 2002 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet* .

Continuation of Attachment(s) 6). Other: Attachment on Deposit of biological Materials.

ATTACHMENT

SUGGESTION FOR DEPOSIT OF BIOLOGICAL MATERIAL

A declaration by applicant or assignee, or a statement by applicant's agent identifying a deposit of biological material and averring the following may be sufficient to overcome an objection or rejection based on a lack of availability of biological material. Such a declaration:

1. Identifies declarant.

2. States that a deposit of the material has been made in a depository affording permanence of the deposit and ready availability thereto by the public if a patent is granted. The depository is to be identified by name and address (See 37 CFR 1.803).

3. States that the deposited material has been accorded a specific (recited) accession number.

4. States that all restrictions on the availability to the public of the material so deposited will be irrevocably removed upon the granting of the patent (See 37 CFR 1.808(a)(2)).

5. States that the material has been deposited under conditions that assure that access to the material will be available during the pendency of the patent application to one determined by the Commissioner to be entitled thereto under 37 CFR 1.14 and 35 USC 122 (See 37 CFR 1.808(a)(1)).

6. States that the deposited material will be maintained with all the care necessary to keep it viable and uncontaminated for a period of at least five years after the most recent request for the furnishing of a sample of the deposited microorganism, and in any case, for a period of at least thirty (30) years after the date of deposit or for the enforceable life of the patent, whichever period is longer. See 37 CFR 1.806.

7. That he/she declares further that all statements made therein of his/her own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United

States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereon.

Alternatively, it may be averred that deposited material has been accepted for deposit under the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure (e.g., see 961 OG 21, 1977) and that all restrictions on the availability to the public of the material so deposited will be irrevocably removed upon the granting of a patent.

Additionally, the deposit must be referred to in the body of the specification and be identified by deposit (accession) number, name and address of the depository, date of deposit and the complete taxonomic description.

DETAILED ACTION

Claims 1-60 are pending in this application.

Specification

Applicant should avoid the use of novel in the title as patents are presumed to be novel and unobvious.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-37, 52-57 and 60 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) Unpredictability of the art. This invention is directed toward a recombinant oncolytic adenoviral vector and its use in gene therapy. Specifically, the vector is comprised of an adenoviral left ITR followed by a termination signal that functions to block adenoviral mediated transcription from the ITR, an E2F responsive promoter linked to a gene essential for replication of the virus, an adenoviral packaging signal and right ITR. Claims 54, 55-57 and 60 read on an *in vivo* method of treating neoplastic conditions by propagation of the oncolytic adenoviral vector in cancer cells such that there is no effect on non-neoplastic cells.

Adenoviral vector use for gene therapy is hindered by the transient nature of the transgene expression coupled with host immune responses. Approaches to prolong transgene expression by multiple injections of adenovirus or to increase transgene expression cause have proven futile in the face of these host immune responses to the recombinant adenoviral vector (Kmiec, p 243 and Anderson, p. 28). Attempts through oncolytic viral therapy to capitalize on the cell-killing or cellular immune response are also thwarted by the humoral immune responses as taught by Verma and Somia; "Unfortunately for gene therapy, most of the human population will probably have antibodies to adenovirus from previous infection with the naturally occurring virus" (Verma and Somia, p 241). And "although it may seem intuitive that a heightened immune response may be good in cancer gene therapy, it is less desirable on a practical scale because the immune response helps to eliminate the vector and to decrease the expression of the transduced gene (p. 4, column 2).

The unpredictability of use of the instantly claimed invention in humans is accentuated by the lack of methods or processes disclosed in the specification. Many parameters must be addressed for *in vivo* use such as tumor cell selectivity in humans, lack of toxicity to normal

tissues, and the effect of the antiviral immune response as well as doses to be administered, dose schedules etc. For example, what level of expression is necessary to achieve therapeutic affects without toxicity to normal cells that results from leaky expression of the viral gene required for replication? The route of delivery itself presents an obstacle to be overcome for the application of the vector therapeutically. Meng and Deiry teach that means of delivery other than intratumoral injection compound the obstacles associated with adenoviral use. "Tropism for organs such as liver, for example by adenovirus, can be a disadvantage if delivery is intended elsewhere or may be advantageous of the liver is the target. Even with regional intravascular administration, the virus must traverse the endothelial wall and travel against pressures within an expanding tumor mass (page 6, column 1). "While reasonably accurate gene delivery can be achieved by direct inoculation of plasmids or recombinant viruses using a needle positioned in a tumour deposit. This strategy achieves a relatively low efficiency of gene delivery, which is confined to tumour cells immediately adjacent to the needle track. Plasmids or viral particles delivered in this way do not permeate freely through the interstitial fluid bathing the tumour." (Russell, p 1165, column 2).

While *in vitro* and animal models have been provided as evidence of success of treatment, *in vitro* results rarely correlate well with *in vivo* clinical trial results in patients and have not translated into successful human therapies. It is not clear that reliance on experimental models accurately reflects the relative superiority or efficacy of the claimed therapeutic strategy and applicants present no disclosed or art recognized nexus between the xenograft and nude mice experimental models and the human disease state. "Although animal studies have suggested low

toxicity and excellent efficacy, these investigation have been limited by the use of immuno-deficienct mice" (Meng and Deiry, p. 6, column 1).

2) State of the art. There has been much interest in the development of oncolytic viruses that capitalize on the lethal effect of adenovirus. However, the lack of established protocols and positive results has hampered the use of such inventions. One of the most studied of these vectors, ONYX015 or dl1520, has not been shown to be effective as a single agent in humans, see Kirn et al, page 6667, column 1, 3rd paragraph. Success with this agent in humans was affected by factors such as effect of the antiviral immune response as well as barriers to intratumoral spread and inadequate viral receptor expression (4th paragraph). Experiments with tumor selective promoters has been disappointing; "it has been reported that certain tumor-specific regulatory elements lose their specificity in the context of an adenoviral vector" (Gomez-Navarro, p 878, column 2).

3) Number of working examples. Applicants disclose no working examples for use of adenoviral vectors to treat diseases in humans.

4) Amount of guidance provided by applicants. No guidance is provided for the administration of the viral vectors in humans. The specification provides as guidance for the delivery of therapeutic genes that the viral vectors are to be administered by direct injection of the vectors in tumors and "In general, the vectors are administered intratumorally in an amount of at least 5x10(9) particles per kilogram body weight and in general, such an amount does not exceed 2.5 x 10(12) particles per kilogram body weight" (page 27, line 24-27). By their own admission (Bergslan et al, 2002), "Even dose administration by body-surface area has been exposed for what it's worth-not much. In other word, although our anticancer armamentarium

keeps increasing, our testing system is imperfect" (page 2220). Therefore, the guidance provided in the specification is not sufficient for the use of the claimed invention.

5) Nature of invention. This invention requires a combination of molecular cloning, viral and cell culture techniques.

6) Level of skill in the art. The level of skill in the art covering this invention was high at the time of invention; however, given the unpredictability of the art, the poorly developed state of the art, the lack of working examples and the lack of guidance provided by applicants, the skilled artisan would have to have conducted undue experimentation to practice the claimed invention.

7) Scope of the invention. This invention has a broad scope in that it recites a method of treatment of any neoplastic condition with an oncolytic adenoviral vector.

In view of predictability of the art to which the invention pertains and the lack of established clinical protocols to predict for whom the therapies would be required: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification for how to reasonably determine how to use the claimed cellular compositions. The claimed vector composition comprising therapeutic genes are include in this rejection because the only disclosed use for these vectors is for gene therapy.

Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue experimentation and excessive experimentation in order to practice the claimed invention.

Claims 10, 13, 23, 24, 26, 30, 31, 33, 35, 37, 44 and 47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants claim a genus of tissue specific promoters derived from the osteolcalcin promoter (claim 13 and 47) and from the human telomerase reverse transcriptase promoter (hTERT) (claim 10 and 44).

Applicant's claims read on a recombinant viral vector comprising a genus of immunostimulatory genes (claims 23 and 24), tumor associated antigen (claim 26), antiangiogenic genes (claim 30, 31 and 35), extracellular matrix protein (claim 33) and suicide genes (claim 37).

The written description requirement for genus claims may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlations between function and structure, or by a combination of such characteristics sufficient to show that the applicant was in possession of the claimed genus. In the instant

application, the applicant teaches use of the mouse osteocalcin promoter (osteolcalcin promoter) and hTERT, SEQ ID 93, and a 245 bp fragment of hTERT, SEQ ID 94. However, there is no actual reduction to practice or clear depiction of what structures or properties are required of promoters derived from the osteocalcin promoter or hTERT to function as tissue-specific promoters. Given the diversity of derivatives and the inability to determine which derivatives will have activity, it is concluded that the invention must be empirically determined. In an unpredictable art, the disclosure of one species would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus.

In the instant case, applicants do not disclose any of the claimed genes. The genomic version of any of the recited genes is not disclosed by the specification nor does the prior art apparently disclose the entire gene. While the cDNAs may be known, not all of the genes have been characterized. Because all of the components of the gene such as regulation sequences, introns, and exons must be determined empirically in order to generate the immunostimulatory genes, tumor associated antigen, antiangiogenic genes, extracellular matrix protein and suicide genes, applicant claims the gene without any disclosure about its structure. The skilled artisan would not conclude that applicant was in possession of viral vector comprising the claimed genes.

Claims 12, 15 and 46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the

invention. Since the specific vectors Ar17pAE2fFTrtex and Ar35E2FE1a, are essential to the claimed invention, they must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public. The invention does not recite use of any vector but instead specifically claims Ar17pAE2fFTrtex and Ar35E2FE1a. The skilled artisan must therefore be able to exactly duplicate these vectors. Applicants note that Ar35E2FE1a vector uses the commercially available pGEN-3z vectors into which applicants insert Ad35 left and right fragments for generation of pFLAd35 from which Ar35E2FE1a is generated. However, commercial availability is not necessarily evidence that the public will have access to the material for the life of a patent (see MPEP 2404.01). pDR2F is used to generate the vector Ar17pAE2fFTrtex. The means to repeatable obtain this vector is not provided in the specification and therefore, the skilled artisan would not be able to reliably reproduce the Ar17pAE2fFTrtex vector. Since neither the instant specification nor the prior art teaches the skilled artisan how to reliably duplicate the Ar17pAE2fFTrtex and Ar35E2FE1a vectors applicants must therefore themselves deposit Ar17pAE2fFTrtex and Ar35E2FE1a recited in the claims and thus satisfy the deposit requirements under 37 CFR 1.801-1.809 (see enclosed Suggestion for deposit of biological material).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 7, 10, 13, 22, 25, 27, 30, 31, 32, 34, 44 and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 is unclear what " corresponding base pairs of other Adenovirus serotypes" encompasses. Do applicants mean the exact nucleotides 103-551 of other serotypes or a deletion of the functions of this region in other serotypes?

Claim 4, 10, 13, 44 and 47 are vague for reciting, "is derived from". It is unclear how closely related the derived sequences are to the original sequences and it is also unclear what procedures were used to derive the claimed sequences. The metes and bounds of the claimed subject are unclear.

Claim 22 recites, "said immunostimulatory gene is a cytokine". Genes are not polypeptides.

Claim 25 recites, "said immunostimulatory gene is a tumor associated antigen." Genes are not polypeptides.

Claim 27 recites, "said immunostimulatory gene is an antibody". Genes are not polypeptides.

Claim 30 recites "said anti-angiogenic gene is selected form the group consisting of a VEGF/VEGFR antagonist...". Genes are not polypeptides.

Claim 31 recites "said anti-angiogenic gene is an inhibitor of PDGF, TGFB or IGF-1." Genes are not polypeptides.

Claim 32 recites "said anti-angiogenic gene is a fragment of an extracellular matrix protein". Genes are not polypeptides.

Claim 34 recites "the anti-angiogenic gene is a fragment of TrpRS." Genes are not polypeptides.

Claims 4, 7, 10, 12, 13, 15, 18-37, 44, 46, 47, 52-57 and 60 are rejected.
Claims 1-3, 5-6, 8, 9, 11, 14, 16, 17, 38-43, 45, 48-51 and 58-59 are allowable.

The prior art does not teach a replication competent adenoviral vector that is comprised of an ITR, a termination signal sequence, E2F responsive promoter linked to a gene essential for viral replication, an adenoviral packaging signal and a right ITR. The invention distinguishes itself from the art by the inclusion of a termination signal following the adenoviral left ITR. The termination signal is meant to interfere with transcription from the ITR that might be initiated in non-neoplastic cells. The E2F promoter is said to be active only in neoplastic cells. The closest art is Application 20030003076 in which an oncolytic adenovirus is generated that is comprised of a left and right ITR, a packaging signal and adenoviral genes required for replication. An E2F promoter is envisioned. However, there is no termination signal 3' to the right ITR.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (703) 605-1207. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-3291.

Maria B Marvich, PhD
Examiner
Art Unit 1636

March 24, 2003

DAVID GUZO
PRIMARY EXAMINER